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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/824,554	MADIYALAKAN ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,9-16 and 22-30* is/are pending in the application.

4a) Of the above claim(s) *1,3-6,9-16 and 26-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 3-6, 9-16 and 22-30 are all the pending claims for this application.

2. Claims 1,3-6,9-16 and 26-30 are withdrawn from examination.

3. Claims 22 and 24 were amended in the Response of 5/8/07.

4. Claims 22-25 are all the pending claims under examination.

Information Disclosure Statement

5. The 1449 form with the IDS of 4/14/2004 lacked a full citation (no volume, page or year) for the reference A6 and the reference CK lacked the volume and/or name of the editor. Applicants have rectified this deficiency in providing the complete information for the references on p. 5 of the Response of 5/8/07.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

6. The rejection of Claims 22-25 for reciting "determining efficacy" is withdrawn. Applicants' allegations that the phrase is defined within the meaning of the claim for an increased T cell response as a result of the xenotypic antibody immunotherapy is found persuasive.

7. The rejection of Claims 22-25 for reciting "favorable determination" is withdrawn in view of the deletion of the phrase and the amendment to recite that the increase in the T cell response is indicative of "the efficacy of said xenotypic antibody-mediated

immunotherapy." Applicants' comments on p. 6 of the Response of 5/8/07 are acknowledged.

8. The rejection of Claim 24 for reciting "T helper cell response is a cytotoxic T cell response" is withdrawn in view of the amendment to delete the term "helper" from the claims. Applicants' comments on p. 6 of the Response of 5/8/07 are acknowledged.

Claim Rejections - 35 USC § 103

9. The rejection of Claims 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madiyalakan et al (WO 97/42973, published 11/20/97) and further in view of Goletz et al (U.S. Patent 5,997,869, issued 12/99) is withdrawn.

As asserted by Applicants' on p. 7 of the Response of 5/8/07, Madiyalakan et al was published as WO 97/42973 and is the international priority application (IB96/00461) with a filing date of 5/15/96 for the instant application. Notably, the parent applications to this application, 09/779,439 and 09/871,339, were copending at the time of filing for the instant application so the chain of priority is maintained.

10. The rejection of Claims 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madiyalakan et al (U.S. Patent 6,241,985, filed 3/20/98) and further in view of Goletz et al (U.S. Patent 5,997,869, issued 12/99) is withdrawn.

As asserted by Applicants' on p. 7 of the Response of 5/8/07, Madiyalakan et al (USPN 6,241,985) is in the chain of priority for the instant application. Notably, the

parent applications to this application, 09/779,439 and 09/871,339, were copending at the time of filing for the instant application so the chain of priority is maintained.

New Grounds for Objection

Specification

11. The specification is objected to for omitting to update the status of the cross-referenced applications in the priority claim. U.S. Application Nos. 09/779,439 and 09/871,339 are abandoned, and PCT Application Number IB96/00461 was published as WO 97/42973.

12. The arrangement of the specification is objected to (see 37 CFR 1.72 (a)). The specification should set forth sections for the summary of the invention, followed by a brief description of the drawings and a detailed explanation or disclosure of the invention. The section entitled "Brief Description of the Drawings" on p. 35 of the specification should be inserted before the section entitled "Disclosure of the Invention" on p. 17.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 22-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 22-25 are indefinite for the recitation "comparing measuring of a T cell response produced by a patient to a target antigen of the xenotypic antibody" in Claim 22 because it is not clear if the target antigen is: an epitope on an antigen, or an antigen (or epitope) on the xenotypic antibody itself. Further, it is not clear whether the T cell response is specific to the antigen recognized by the xenotypic antibody or to a xenotypic antibody/antigen complex where the T cell epitope is separate from the antibody epitope.

See for example, Claims 1-3 of Applicant's patent, USPN 6,241,985, where the claimed method of administering the same B43.13 xenotypic antibody disclosed in the instant specification, binds to the CA125 antigen to produce a host cellular immune response, which encompasses a T cell response, and where a second epitope on the antigen elicits the cellular immune response.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

14. Claims 22-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims encompass xenotypic antibodies that are not described in the specification.

Claims 22-25 are drawn to a method of determining the efficacy of any xenotypic antibody-mediated immunotherapy, where the efficacy is measured by an increase in T cell response after administering the antibody to any patient where the T cell response is produced to any antigen recognized by the antibody and an increase over the T cell response measured prior to antibody administration is indicative of the efficacy of the xenotypic antibody, where the T cell response is a T helper response or a cytotoxic T cell response, and the patient is human.

The claims encompass any genus of xenotypic antibodies useful for inducing a T cell response to any antigen in any patient. Therefore, the claims encompass a genus of xenotypic antibodies defined solely by its principal biological property (T cell-inducing), which is simply a wish to know the identity of any material with that biological property. The specification discloses three classes of antigen against which a xenotypic antibody could theoretically be used in the method invention on p. 18, lines 5-13:

B43.13, recognizes ovarian cancer antigen CA 125 at the 43.13 epitope;

a binding agent for CA19.9 a gastrointestinal cancer antigen; and

a binding agent for CA15.3 a breast cancer antigen.

Notably, the specification does not even disclose any examples of specific xenotypic antibodies generated against the CA19.9 and CA15.3 antigens. The specification only describes using the B43.13 antibody in a method to determine the efficacy of the antibody vis-à-vis induction of a T cell response against CA 125 (Example 4 (in vitro mouse study measuring T cell proliferation) and Examples 8 and 9 (in vivo human study measuring induction of CA125 specific CTL's)).

Accordingly, there is insufficient written description encompassing a xenotypic antibody against a target antigen because the relevant identifying characteristics of the genus of xenotypic antibodies such as structure or other physical and/or chemical characteristics of an efficacious "xenotypic antibody" are not set forth in the specification as-filed, commensurate in scope with the claimed invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function" and the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity and which therefore, fails to satisfy the written description requirement. Similarly, a xenotypic antibody useful for inducing a T cell response against an antigen recognized by the antibody in a patient does not distinguish any particular xenotypic antibody (e.g., a particular antibody such as B43.13) from others having the same activity or function and as such does not satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

In the absence of structural characteristics that are shared by members of the genus of a xenotypic antibody useful for inducing an increase in a T cell response against any antigen recognized by the antibody in any patient; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed

genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Scope of Enablement

15. Claims 22-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of measuring the efficacy of a xenotypic antibody, Mab B43.13, vis-à-vis the increase in T cell response (e.g., T cell proliferation, CTL induction and cytotoxicity) in ovarian cancer patients administered low dose antibody, does not reasonably provide enablement for measuring the T cell response-inducing efficacy of just any xenotypic antibody as an intended immunotherapy against just any antigen in just any patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Nature of the Invention/ Skill in the Art

The interpretation of Claims 22-25 is discussed supra.

The skill in the art required to practice the claimed invention is that of a clinician with the ability to manage any disorder in any patient using any xenotypic antibody immunotherapy, where the xenotypic antibody is directed against any antigen.

Disclosure in the specification

See the interpretation of the disclosure in the specification as discussed supra under section 14. Based on the limited disclosure in the specification for practicing the method invention with the genus of xenotypic antibodies encompassed by the claims,

one skilled in the art would be required to perform undue trial and error experimentation in obtaining any xenotypic antibody against a relevant antigen that was sought to be targeted in a patient, and where the endpoint of the method was to assess whether the patient developed an increase in any T cell response against the antigen over the T cell response measured in the same patient prior to the administration of the antibody.

Notably, Applicants own specification discusses and appreciates the limitations of administering a xenotypic antibody in a human patient (e.g., mouse antibody to human) where the resultant effect is HAMA. On pp. 13, line 4- p. 14, line 2, the contraindications for xenotypic immunotherapy are outlined as 1) increasing risk of anaphylaxis, 2) interference with subsequently injected mouse antibodies (complexing, increased clearance, reduce tumor localization, enhanced liver and spleen uptake, and tumor masking), and 3) blocking immunodiagnostic agents for disease progression and treatment course. Further on, the specification teaches away from using the mouse 17-1A Mab in Duke's stage C colorectal cancer patients on p. 14, lines 1-2.

On p.19, at lines 24-31, the specification discloses single chain antibodies and fragments of Mabs. In Table 1 on p. 27, the results from Applicants human patient study *appear* to have used a single chain Mab B43.13 and F(ab)' Mab B43.13 to avoid HAMA (see footnote to Table 1) and for comparison of antibody induction. The examples (Ex. 8 and 9) describing results for T cell induction in the patient study are presumed to have used the same population of ovarian cancer patients and the same single chain Mab B43.13 and F(ab)' Mab B43.13.

Thus in viewing the disclosure in the specification as a whole, one skilled in the art would not have been motivated to have used just any xenotypic antibody as an immunotherapeutic in just any patient at the time of filing (1996) in a method to assess the efficacy of the antibody against any antigen by measuring an increase in a T cell response to the same antigen. The scope of the claims encompass embodiments that are not only non-enabled but which are specifically discouraged by Applicants own specification.

Teaching in the art regarding xenotypic antibody immunotherapy

As of 1995 and just prior to the application filing date, in the field of immunotherapeutics it was recognized that in order to reduce the HAMA associated with a xenotypic antibody in a subject, that modified forms of the antibody could be generated that reduced the overall non-specific immunogenicity of the antibody such as taught by Queen (USPN 5,530,101; chimeric and humanized antibodies).

However, for the instant xenotypic murine Mab B43.13 (oregovomab, OvaRex®, AltaRex) of the application, Berek (Exp. Op. Biol. Ther. 4(7): 1159-1165) reviewed the history and clinical trial outcomes for the antibody in 2004. Berek set the background for the failure of various immunotherapeutic approaches being attributable to downregulation of autoreactive B and T cells (p. 1160, Col. 1, ¶3) and that clinical development of Mab B43.13 was reflective of those challenges. Berek describes the induction of antibody responses (HAMA) in more than 90% of patients to oregovomab with specificity for Ig constant regions and variable domain idiotopes (p. 1161, Col. 1, ¶2), but that in two patient studies some patients produced an increase in tumour-

specific INF-γ-producing reactive T cells (p. 1161, Col. 2, ¶ 2). Thus despite the induction of HAMA, oregovomab when administered *at low doses* compared to other immunotherapeutics, shows promise in initiating cellular immunity directed against CA 125 and its tumor cells of origin in a limited number of clinical trials.

Therefore, in view of the lack of guidance and lack of examples of xenotypic antibodies in the specification, and lack of predictability associated with regard to using myriad xenotypic antibodies for intended immunotherapy and having a T cell-inducing property effect in any patient against an antigen recognized by the xenotypic antibody encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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